(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 426 066 A2**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 90120698.7

(51) Int. Cl.5: A61K 31/40

(22) Date of filing: 29.10.90

(30) Priority: 30.10.89 US 429119

(43) Date of publication of application:
08.05.91 Bulletin 91/19

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

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(54) Ace inhibitors for use for preventing onset of type II diabetes.

(57) A method is provided for preventing onset of Type II diabetes in hypertensive or normotensive patients and thereby preventing atherosclerotic lesions in such patients in a mammalian species by administering an ACE inhibitor, especially one containing a mercapto moiety, such as captopril or zofenopril.

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ACE INHIBITORS FOR USE FOR PREVENTING ONSET OF TYPE II DIABETES

The present invention relates to the use of an ACE inhibitor, preferably an ACE inhibitor containing a mercapto moiety, such as captopril or zofenopril for the preparation of a pharmaceutical composition for preventing onset of Type II diabetes in mammalian species.

It has been found that angiotensin converting enzyme inhibitors, especially mercapto containing ACE inhibitors such as captopril and zofenopril, are capable of reducing insulin resistance in hypertensive patients, in patients with impaired glucose tolerance, in obese patients and in normotensive patients of normal weight, and thereby prevent onset of Type II diabetes in such patients.

In accordance with the present invention, a method is provided for preventing onset of Type II diabetes, and thereby prevent onset of coronary artery disease and prevent onset of atherosclerosis in mammalian species, wherein a therapeutically effective amount of angiotensin converting enzyme inhibitor is administered systemically, such as orally or parenterally.

The ACE inhibitor may be administered to hypertensive patients or normotensive patients in accordance with the method of the present invention.

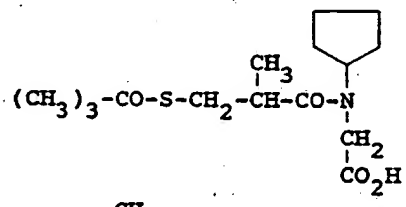
The method of the invention will preferably be carried out on hypertensive patients, patients with impaired glucose tolerance, obese patients as well as normotensives having insulin resistance or hyperinsulinemia.

The term "insulin resistance" or "hyperinsulinemia" as employed herein refers to a condition wherein higher than normal insulin concentrations are required to maintain normal glucose levels.

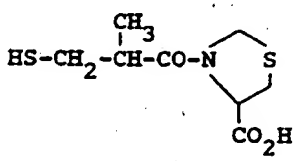
In preferred embodiments where the patient to be treated in accordance with the present invention is normotensive, the angiotensin converting enzyme inhibitor will preferably be administered in amounts below that required to cause hemodynamic effects, that is below that required to cause a reduction in blood pressure. Where the patinet to be treated is hypertensive, then the angiotensin converting enzyme inhibitor will be employed in amounts usually employed to treat hypertension.

The angiotensin converting enzyme inhibitor which may be employed herein preferably includes those containing a mercapto (-S-) moiety such as substituted proline derivatives, such as any of those disclosed in US-A- 4,046,889 to Ondetti et al mentioned above, with captopril, that is, 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, being preferred, and mercaptoacyl derivatives of substituted prolines such as any of those disclosed in US-A-4,316,906 with zofenopril being preferred.

Other examples of mercapto containing ACE inhibitors that may be employed herein include rentiapril (fentiapril, Santen) disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983); as well as pivopril, that is



and YS980, that is



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Other examples of angiotensin converting enzyme inhibitors which may be employed herein include any of those disclosed in US-A-4, 374, 829 mentioned above, with N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline, that is, enalapril, being preferred, any of the phosphonate substituted amino or imino acids or salts disclosed in US-A- 4, 452, 790 with (S)-1-[6-amino-2-[[hydroxy-(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline (SQ 29,852 or ceranapril) being preferred, phosphinylalkanoyl prolines disclosed in US-A- 4,1680,267 mentioned above with fosinopril being preferred, any of the phosphinylalkanoyl substituted prolines disclosed in US-A-4,337,201, and the phosphonamidates disclosed in US-A-4,432,971 discussed above.

Other examples of ACE inhibitors that may be employed herein include Beecham's BRL 36,378 as

disclosed in European patent Nos. 80822 and 60668; Chugai's MC-838 disclosed in CA. 102:72588v and Jap. J. Pharmacol. 40:373 (1986); Ciba-Geigy's CGS 14824 (3-([1-ethoxycarbonyl-3-phenyl-(1S)-propyl]-amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCl) disclosed in U.K. Patent No. 2103614 and CGS 16,617 (3(S)-[[(1S)-5-amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid) disclosed in US-A-4,473,575;cetapril (alacepril, Dainippon) disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986); ramipril (Hoechst) disclosed in EP-A- 79-022 and Curr. Ther. Res. 40:74 (1986); Ru 44570 (Hoechst) disclosed in Arzneimittelforschung 35:1254 (1985), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987); R_o 31-2201 (Hoffman-LaRoche) disclosed in FEBS Lett. 165:201 (1984); lisinopril (Merck) disclosed in Curr. Therap. Res. 37:342 (1985) and EP-A-12-401, indalapril (delapril) disclosed in U. S. Patent No. 4,385,051; indolapril (Schering) disclosed in J. Cardiovasc. Pharmacol. 5:643, 655 (1983); spirapril (Schering) disclosed in Acta. Pharmacol. Toxicol. 59 (Supp. 5):173. (1986); perindopril (Servier) disclosed in Eur. J. Clin. Pharmacol. 31:519 (1987); quinapril (Warner-Lambert) disclosed in US-A-4,344,949 and CI 925 (Warner-Lambert) ([3S-[2[R(*)R(*)]]3R(*)]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino[-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid HCl) disclosed in Pharmacologist 26:243, 266 (1984), WY-44221 (Wyeth) disclosed in J. Med. Chem. 26:394 (1983).

Preferred are those ACE inhibitors which are proline or substituted proline derivatives and most preferred are such ACE inhibitors which include a mercapto group.

The above-mentioned U.S. patents are incorporated herein by reference.

In carrying out the method of the present invention, the angiotensin converting enzyme inhibitor may be administered to mammalian species, such as horses, cattle, dogs, cats, and humans, and as such may be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable, as well as suppository dosage forms that release ACE inhibitor in the bloodstream. The above dosage forms will also include the necessary carrier material, excipient, lubricant, buffer, bulking agent (such as mannitol), antioxidants (ascorbic acid of sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms such as intramuscular, intraperitoneal, or intravenous enema and suppository forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

Thus, for oral administration, a satisfactory result may be obtained employing the ACE inhibitor in an amount within the range of from about 0.01 mg/kg to about 100 mg/kg and preferably from about 0.1 mg/kg to about 25 mg/kg.

A preferred oral dosage form , such as tablets or capsules, will contain the ACE inhibitor in an amount of from about 0.1 to about 500 mg, preferably from about 2 to about 200 mg, and more preferably from about 3 to about 150 mg.

For parenteral administration, the ACE inhibitor will be employed in an amount within the range of from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.01 mg/kg to about 1 mg/kg.

The composition described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose and work up gradually to a high dose.

Tablets of various sizes can be prepared, e.g., of about 5 to 700 mg in total weight, containing the active substance in the range described above, with the remainder being a physiologically acceptable carrier of other materials according to accepted pharmaceutical practice. These tablets can, of course, be scored to provide for fractional doses. Gelatin capsules can be similarly formulated.

Liquid formulations can also be prepared by dissolving or suspending the active substance in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage in one to four teaspoonfuls.

Such dosage forms can be administered to the patient on a regimen of one to four doses per day.

Suppository formulations containing from about 5 to about 250 mg ACE inhibitor may be prepared as well using a conventional suppository base (such as disclosed in US-A-4,344,968, 4,265,875, and 4,542,020) so as provide the desired dosage in one to four suppositories per day.

As indicated, where the patient to be treated is normotensive, then smaller amount of angiotensin converting enzyme inhibitor preferably will be employed, that is below that required to reduce blood pressure. For example, for oral dosage forms, normotensives may be treated with from about 0.01 mg/kg to about 1 mg/kg or from about 1 mg to about 6 mg, one to four times daily.

In formulating the compositions, the active substances, in the amounts described above, are compounded according to accepted pharmaceutical practice with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in the particular type of unit dosage form.

Illustrative of the adjuvants which may be incorporated in tablets are the following: a binder such as

gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate or cellulose; a disintegrating agent such as corn starch, potato starch, alginic acid or the like; a lubricant such as stearic acid or magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as orange, peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac, sugar or both. A syrup of elixir may contain the active compound, water, alcohol or the like as the carrier, glycerol as solubilizer, sucrose as sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange.

The formulations as described above will be administered for a prolonged period, that is, for as long as it is necessary to prevent Type II diabetes. Sustained release forms of such formulations which may provide such amounts biweekly, weekly, monthly and the like may also be employed. A dosing period of at least one to two weeks are required to achieve minimal benefit.

The following Examples represent preferred embodiments of the present invention.

Example 1

A captopril formulation suitable for oral administration in preventing onset of Type II diabetes in hypertensive or normotensive patients and preventing coronary atherosclerotic lesions in such patients is set out below.

1000 tablets each containing 100 mg of 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline were produced from the following ingredients.

1-[(2S)-3-Mercapto-2-methylpropionyl]-L-proline (captopril)	100 g
Corn starch	50 g
Gelatin	7.5 g
Avicel (microcrystalline cellulose)	25 g
Magnesium stearate	2.5 g

The captopril and corn starch are admixed with an aqueous solution of the gelatin. The mixture is dried and ground to a fine powder. The Avicel and then the magnesium stearate are admixed with the granulation. This is then compressed in a tablet to form 1000 tablets each containing 100 mg of active ingredient which is used for preventing onset of Type II diabetes as described above.

Example 2

1000 tablets each containing 200 mg of captopril are produced from the following ingredients:

Captopril	200 g
Lactose	100 g
Avicel	150 g
Corn starch	50 g
Magnesium stearate	5 g

The captopril, lactose and Avicel are admixed, then blended with the corn starch. Magnesium stearate is added. The dry mixture is compressed in a tablet press to form 1000 505 mg tablets each containing 200 mg of active ingredient. The tablets ar coated with a solution of Methocel E 15 (methyl cellulose) including as a color a lake containing yellow #6. The resulting tablets are useful in preventing onset of Type II diabetes in hypertensive or normotensive patients and preventing coronary atherosclerotic lesions in such patients.

Example 3

Two piece #1 gelatin capsules each containing 5 mg of captopril are filled with a mixture of the following ingredients:

Captopril	5 mg
Magnesium stearate	7 mg
USP lactose	193 mg.

The resulting capsules are useful in preventing onset of Type II diabetes in normotensive patients and preventing coronary atherosclerotic lesions in such patients.

Example 4

An injectable solution for use in preventing onset of Type II diabetes in hypertensive or normotensive patients and preventing coronary atherosclerotic lesions in such patients.

Captopril	500 mg
Methyl paraben	5 mg
Propyl paraben	1 mg
Sodium chloride	25 g
Water for injection qs.	5 l.

The captopril, preservatives and sodium chloride are dissolved in 3 liters of water for injection and then the volume is brought up to 5 liters. The solution is filtered through a sterile filter and aseptically filled into presterilized vials which are then closed with presterilized rubber closures. Each vial contains 5 ml of solution in a concentration of 100 mg of active ingredient per ml of solution for injection.

Example 5 to 8

Dosage forms for use in preventing onset of Type II diabetes in hypertensive or normotensive patients and preventing coronary atherosclerotic lesions in such patients are prepared as described in Examples 1 to 4 except that N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline (enalapril) is used in place of captopril.

Example 9 and 10

A suppository formulation containing conventional suppository base such as any of those disclosed in US-A-4,344,960, 4,26 5,875 or 4,542,020, and N-(1-ethoxy-carbonyl-3-phenylpropyl)-L-alanyl-L-proline (40 mg), (enalapril) or captopril (25 mg), is prepared and is used to prevent onset of Type II diabetes in hypertensive or normotensive patients and preventing coronary atherosclerotic lesions in such patients.

Example 11

A zofenopril formulation suitable for oral administration in preventing onset of Type II diabetes in

hypertensive or normotensive patients and preventing coronary atherosclerotic lesions in such patients is set out below.

1000 tablets each containing 100 mg of zofenopril are produced from the following ingredients.

[1(S),4(S)]-1-[3-(benzoylthio)-2-methyl-1-oxopropyl-4-(phenylthio)-L-proline (zofenopril)	100 g
Corn starch	50 g
Gelatin	7.5 g
Avicel (microcrystalline cellulose)	25 g
Magnesium stearate	2.5 g

The zofenopril and corn starch are admixed with an aqueous solution of the gelatin. The mixture is dried and ground to a fine powder. The Avicel and then the magnesium stearate are admixed with the granulation. This is then compressed in a tablet to form 1000 tablets each containing 100 mg of active ingredient which is used for treating atherosclerosis as described above.

Example 12

A modified release beadlet formulation capable of slowly releasing the angiotensin converting enzyme inhibitor captopril over a period of up to 6 hours and having the following composition was prepared as described below.

Ingredient	Amount in Parts by Weight
Captopril	27
Citric aicd	30
Microcrystalline cellulose*	43

*amount may vary to reflect chemical purity of captopril

The above ingredients were mixed and kneaded using water in a planetary mixer to form a wet mass. The wet mass was passed through a Nica E140 extruder to form an extrudate (~1 mm diameter). The extrudate was then passed through a Nica spheronizer to form beadlets. The beadlets were then dried at 40° C for 12-18 hours in a tray drying oven or for 2-4 hours in a fluid bed dryer. A fraction of the so-formed beadlets were filled into hard shell pharmaceutical capsules for use in preventing onset of Type II diabetes in hypertensive or normotensive patients and preventing coronary atherosclerotic lesions in such patients.

Example 13

A modified release coated-beadlet formulation having the following composition was prepared as follows.

(i)	Core	mg/dose
	Captopril	5 mg
	Microcrystalline cellulose	159.1 mg
	Citric acid	37. mg
	Lactose	74.1 mg
(ii)	Sealcoat	
	Hydroxypropyl methyl cellulose ca.	8.3 mg
	Polyethylene glycol ca.	2.8 mg
(iii)	Barriercoat	
	Cellulose acetate phthalate ca.	4.2 mg
	Acetylated monoglycerides (Myvacet®9-40) ca.	1.3 mg

The beadlet cores were prepared as described in Example 12. After the dried beadlets were formed, they were coated via a two step process as follows. An aqueous solution of hydroxypropyl methyl cellulose (7.5% by weight) and polyethylene glycol (2.5% by weight) was prepared and sprayed on to the beadlets to form a sealcoat. The beadlets were then coated with a barriercoat using an aqueous dispersion of cellulose acetate phthalate (30% by weight) mixed with acetylated monoglycerides (9.5% by weight).The beadlets were then filled into hard shell pharmaceutical capsules which are useful in preventing onset of diabetes of Type II diabetes in normotensive patients and preventing coronary atherosclerotic lesions in such patients.

Example 14

A modified release coated-beadlet formulation having the following composition was prepared as follows.

Ingredient	% by Weight of Coated Beadlet
Core	
Captopril	26.2
Citric acid	29.1
Microcrystalline cellulose	41.8
Film coating	
Hydroxypropylmethyl cellulose phthalate ca.	2.6
triethyl citrate ca.	0.3

The beadlet cores were prepared as described in Example 12.

Hydroxypropylmethyl cellulose phthalate (9 parts) and triethylcitrate (1 part) were dissolved in ethyl alcohol (90 parts) and then sprayed on to the beadlets to form coated product. The so-formed beadlets were then filled into hard shell pharmaceutical capsules which are useful in preventing onset of Type II diabetes in hypertensive or normotensive patients and preventing coronary atherosclerotic lesions in such patients.

Examples 15 to 19

Following the procedure of Examples 13 to 15 except substituting the following ACE inhibitor, organic acid and binder-excipients, the following beadlet compositions may be prepared which are useful in

preventing onset of Type II diabetes in hypertensive or normotensive patients and preventing coronary atherosclerotic lesions in such patients.

Ex. No.	ACE Inhibitor	Organic acid	Binder
15.	N-(1-ethoxycarbonyl-3-phenylpropyl)-L-proline	Citric acid	Microcrystalline cellulose
16.	(S)-1-[6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline	Malic acid	Microcrystalline cellulose and hydroxypropyl methyl cellulose
17.	Lisinopril	Tartaric acid	Na carboxymethyl cellulose
18.	Zofenopril	Succinic acid	Gelatin, pectin and Na carboxymethyl cellulose
19.	Fosinopril	Maleic acid	Microcrystalline cellulose

Example 20

By substituting 5 g of pivopril for the zofenopril in Example 11, 1000 tablets each containing 5 mg of the pivopril are produced which is useful in preventing onset of Type II diabetes in normotensive patients and preventing coronary atherosclerotic lesions in such patients.

Example 21

1000 tablets each containing 200 mg of YS890 are produced from the following ingredients:

YS890	200 g
Lactose	100 g
Avicel	150 g
Corn starch	50 g
Magnesium stearate	5 g

The YS890, lactose and Avicel are admixed, then blended with the corn starch. Magnesium stearate is added.The dry mixture is compressed in a tablet press to form 1000 505 mg tablets each containing 200 mg of active ingredient. The tablets are coated with a solution of Methocel E 15 (methyl cellulose) including as a color a lake containing yellow #6. The resulting tablets are useful in preventing onset of Type II diabetes in hypertensive or normotensive patients and preventing coronary atherosclerotic lesions in such patients.

Claims

1. The use of an angiotensin converting enzyme inhibitor for preparing a pharmaceutical composition for preventing onset of Type II diabetes in a mammmlian species.
2. The method as defined in claim 1 wherein the angiotensin converting enzyme inhibitor is a mercapto containing angiotensin converting enzyme inhibitor.
3. The method as defined in claim 1 wherin the angiotensin converting enzyme inhibitor is a substituted proline derivative.
4. The use as defined in claim 1 wherin said angiotensin converting enzyme inhibitor includes a mercapto moiety and is a substituted proline derivative.
5. The use as defined in claim 1 wherein the angiotensin converting enzyme inhibitor is a phosphonate substituted amino or imino acid or salt thereof, a proline derivative,
6. The use as defined in claim 1 wherein said angiotensin converting enzyme inhibitor is a phosphinylalkanoyl proline derivative, a phosphoramidate derivative, or a phosphonate substituted amino or imino acid or salt thereof.
7. The use as defined in claim 1 wherein said angiotensin converting enzyme inhibitor is a captopril.
8. The use as defined in claim 1 wherein said angiotensin converting enzyme inhibitor is zofenopril.
9. The use as defined in claim 1 wherein said angiotensin converting enzyme inhibitor is fentiapril.
10. The use as defined in claim 1 wherein said angiotensin converting enzyme inhibitor is enalapril or lisinopril.
11. The use as defined in claim 1 wherein said angiotensin converting enzyme inhibitor is fosinopril or (S)-1- [6-amino-2-[[hydroxy(4-phenyl-butyl)phosphinyl]oxy]-1-oxohexyl]-L-proline (ceranapril).
12. The use as defined in claim 1 wherein said pharmaceutical composition is formulated for oral or parenteral administration.
13. The use as defined in claim 12 wherein said administration of the angiotensin converting enzyme inhibitor is below that amount required to effect a reduction in blood pressure.

14. The use of an angiotensin converting enzyme inhibitor for preparing a pharmaceutical composition for preventing onset of atherosclerosis in a mammalian species.

15. The use of an agiotensin converting enzyme inhibitor for preparing a pharmaceutical composition for preventing onset of coronary artery disease in a mammalian species.